

The Effectiveness of Dynamic Contrast Enhanced MRI and Diffusion Weighted MRI for Evaluating Early Treatment Response of Locally Advanced Breast Cancer to Neoadjuvant Chemotherapy

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Purpose: To clarify whether dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and diffusion-weighted magnetic resonance imaging (DWI) performed after two cycles of neoadjuvant chemotherapy can be used to predict pathologic complete response (pCR) in patients with breast cancer.

Materials and Methods: Fourteen women who had DCE-MRI and DWI prior to and after two cycles of neoadjuvant chemotherapy due to breast cancer in same consoles had been included. Lesion size and degree of peak enhancement derived from DCE-MRI, and the apparent diffusion coefficient (ADC) value derived from ADC mapping were compared between lesions with and without pathologic complete response (pCR). Interval changes in lesion size, degree of peak enhancement, and ADC value before and after two cycles of chemotherapy were compared.

Results: The initial lesion size with pCR was smaller than those without (P value, 0.855). The initial peak enhancement and ADC value of lesions with pCR was lower than those without, but not significantly different (P values, 0.770 and 0.660). The size and peak enhancement of lesions with pCR were significantly decreased compared with those without (P value, 0.045 and 0.044). The ADC value of lesions with pCR was increased compared with lesions without, but not statistically significant (P value, 0.132).

Conclusion: The lesion size and the degree of peak enhancement were significantly reduced in lesions with pCR after two cycles of neoadjuvant chemotherapy, but a large-scale study is anticipated.

Index words: Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI);
Diffusion weighted magnetic resonance imaging (DWI); Pathologic complete response (pCR);
Breast cancer; Neoadjuvant chemotherapy

Introduction

Application of neoadjuvant chemotherapy has increased in women with primary breast malignancies to down-stage the tumor and to enable successful breast conservation surgery. It has been established that patients with pathologic complete response (pCR) have a favorable prognosis (1–3). The early recognition of response to neoadjuvant chemotherapy is important for optimal management, avoiding ineffective and toxic therapy in non-responding patients. Unfortunately, how to monitor the response to neoadjuvant chemotherapy in breast cancer patients has not been established. In the RECIST (Response Evaluation Criteria In Solid Tumors), longest diameter of lesions are measured for estimating treatment response (4). This response assessment, however, is usually based on morphologic changes in size that occur after physiological changes within the tumor (5, 6). Functional magnetic resonance imaging (MRI) related to dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) or diffusion-weighted magnetic resonance imaging (DWI) has its advantages over traditional assessment methods and is currently available to detect changes in the tumor microenvironment prior to any morphological change (7).

Therefore, the purpose of our study is to clarify whether DWI and DCE-MRI performed after two cycles of neoadjuvant chemotherapy can be used to predict pathologic complete response (pCR) in patients with breast cancer.

Materials and Methods

Patients, treatment and response assessment

Institutional committees on clinical research and ethics approval and patient consent were obtained. From January 2012 to July 2012, 14 patients who had been diagnosed with invasive ductal carcinoma on core needle biopsy with MRI examinations performed in the same consoles were included. MRI examinations were performed twice for each patient, once before neoadjuvant chemotherapy and once after two cycles of chemotherapy. Patients underwent chemotherapy using the following regimen, adriamycin (60 mg/m²) and cy-

toxan (600 mg/m²) intravenously approximately every 3 weeks. After neoadjuvant chemotherapy, nine patients underwent conservation surgery and five underwent total mastectomy. Postoperative radiation treatment with or without adjuvant chemotherapy were performed.

MR Image Acquisition and Data Analysis

DCE-MRI and DWI were obtained using 3-T whole-body magnet system (Magnetom Trio, A Tim System; Siemens Healthcare, Erlangen, Germany) equipped with a dedicated breast coil. Gadoterate meglumine (Gd-DOTA; Dotarem; Guerbet, Roissy CdG Cedex, France) was used as contrast media at a dose of 0.1 mmol/kg. Gd-DOTA was injected intravenously at a rate of 3.0 mL/sec followed by a 20-mL normal saline Flush by an automatic injector (Sonicshot GX; Nemoto Kyorindo, Kyoto, Japan). Six contrast-enhanced image series with axial sections were obtained for both breasts with a time interval of 60 seconds after intravenous injection of contrast. Pre-contrast images of the dynamic series were subtracted from the post-contrast images through image processing. DWI was acquired using a DW echo-planar imaging sequence with parallel imaging. Apparent diffusion coefficient (ADC) mapping and post-processing images were obtained based on DW images with b values of 0 and 600 s/mm². ADC maps were calculated and ADC values were derived on a voxel-by-voxel basis as follows: $ADC = (1/b) \times \ln(S_0/S)$.

DCE MR and DWI were analyzed with CADstream software (version 5.2.8.591, Merge Healthcare, Milwaukee, WI, USA). The degree of peak enhancement of the lesion was determined to show the strongest enhancement within the lesion compared to pre-contrast images and was automatically obtained through CADstream software at the targeted lesion. The lesion size (transverse diameter, longitudinal diameter, and height) was derived from DCE-MRI 2 minutes after intravenous injection of contrast using CADstream software. The region of interest (ROI) was manually drawn on the ADC map and the ADC value of the lesion was depicted by a voxel using CADstream software. ADC values were measured three times per lesion and their mean value was used for analysis.

Data and Statistical Analyses

The pCR was defined as the status without residual invasive cancer regardless of the histological type of in situ component. The patients were classified into two groups, pCR or not. Mann-Whitney U tests were used to compare the patients' age, initial lesion size, degree of peak enhancement, and ADC values between two groups. The association between interval change of size, degree of peak enhancement, and ADC values after two cycles of neoadjuvant chemotherapy and pCR were also evaluated using Mann-Whitney U test. Statistical analysis was performed with the SPSS® statistical software (SPSS Inc., Chicago, IL, ver 20.0). Two-sided P value < 0.05 was considered to be indicative of statistical significance.

Results

The median age of 14 patients was 55.5 years (range,

29–64). Two patients (14.29%) achieved pCR and 12 (85.7%) had residual invasive ductal carcinoma in their surgical specimens. The median age of patients with pCR was 55.5 years, not significantly different to those without, 45.5 years (P value, 0.552) (Table 1). The median size of lesions with pCR was 24.5 mm, smaller than those without, 26.0 mm (P value, 0.855). The peak enhancement of lesions with pCR was 160.5%, not significantly different to 177.0% (P value, 0.770). The ADC value of lesions with pCR was 1.145×10^{-3} mm²/sec, lower than 1.355×10^{-3} mm²/sec of those without, but not significantly different (P value, 0.660).

After two cycles of neoadjuvant chemotherapy, the median lesion size and peak enhancements were decreased, and the ADC values were increased (Table 2).

The lesion size with pCR was significantly decreased compared with those without (P value, 0.045) (Table 3). The peak enhancement of lesions with pCR was decreased by 68.6%, whereas interval decrease in lesions

Table 1. The Comparisons of Initial Lesion Size, Degree of Peak Enhancement, and ADC Values According to the Pathological Complete Response

	Pathologic CR (n = 2)	Not pathologic CR (n = 12)	P value
Median age (years)	55.5	45.5	0.552
Median size (mm)	24.5	26	0.855
Median peak enhancement (%)	160.5	177	0.770
Median ADC ($\times 10^{-3}$ mm ² /sec)	1.145	1.355	0.660

ADC: apparent diffusion coefficient

CR: complete response

Table 2. The Interval Changes of Lesion Size, Degree of Peak Enhancement, and ADC Values After 2 Cycles of Neoadjuvant Chemotherapy

	Pre-chemotherapy	After 2 cycle of chemotherapy	Interval change
Median size (mm)	25.5	16.5	–25%
Median peak enhancement (%)	167	156	–15.8%
Median ADC ($\times 10^{-3}$ mm ² /sec)	1.355	1.55	13.7%

ADC: apparent diffusion coefficient

Table 3. The Comparisons of Interval Changes in Lesion Size, Degree of Peak Enhancement, and ADC Values After 2 Cycles of Neoadjuvant Chemotherapy According to the Pathological Complete Response

	Pathologic CR	Not pathologic CR	P value
Change of median size (%)	–78.6	–23.5	0.0446
Change of median peak enhancement (%)	–68.6	–13.2	0.0440
Change of median ADC (%)	83.3	10.9	0.1319

ADC: apparent diffusion coefficient

CR: complete response

without pCR was only 13.2% (P value, 0.044). The ADC value of lesions with pCR was increased by 83.3%, higher than 10.9% of those without, but without statistical significance (P value, 0.132).

Discussion

Patients with locally advanced breast cancer will be treated initially with neoadjuvant chemotherapy to down-stage the disease, followed usually by surgery and post-operative therapies (8, 9). Patients with pCR after neoadjuvant chemotherapy have better disease-free and overall survival rates (8, 10). To achieve pCR and to avoid ineffective treatment, identification of early response after treatment is important. Traditionally, clinical examination and conventional imaging techniques, such as mammography and breast ultrasound, have been used to assess tumor size for estimating treatment response. Many studies have shown, however, that clinical examination, mammography, and ultrasonography are imperfect techniques for assessing tumor size and response to neoadjuvant chemotherapy (11–13). MRI has been shown to be superior to the conventional breast imaging modalities in both the initial staging of primary breast cancer (14–17) and in the assessment of residual disease at the end of neoadjuvant chemotherapy (16, 18–20), especially in non-mass lesions or tumors that have fragmented into many foci (21).

Functional MRI such as DCE MRI and DWI are available for assessing early treatment response (7). Studies using DCE-MRI has suggested that the morphologic changes in size and magnitude of enhancement were associated with histological responses to treatment (22–25). DCE-MRI specifically predicts pCR after neoadjuvant chemotherapy in breast cancer patients (26). We found that the breast cancer lesions with pCR showed significant reduction of the peak enhancement after two cycles of neoadjuvant chemotherapy compared with those without pCR (P value, 0.0440), which is comparable to previous studies (22–25). DCE-MRI permits evaluation of tumor neovasculature, thereby allowing an assessment of the pathophysiological response to therapy, which occurs prior to any volume or size changes (27). Quantification of blood flow within a tumor by using DCE-MRI has been reported to provide

accurate information while monitoring the effects of chemotherapy in patients with breast cancer (28).

The change in ADC values also precedes tumor size change (23, 29, 30). Wu's meta-analysis has confirmed that DWI is a sensitive modality in predicting pCR to neoadjuvant chemotherapy in breast cancer patients (26). In our study, the ADC value in lesions with pCR has increased more than those without but not without significance (P value, 0.132). This is concordant to the trends reported in other studies (23, 28, 31, 32). Areas with low tumor cellularity due to cellular damage and necrosis after neoadjuvant chemotherapy are less resistant to the diffusion of water molecules, which corresponds to a higher ADC and an increase in ADC (31).

Although it has been recognized that size change is a less accurate assessment method in predicting the effects of neoadjuvant chemotherapy (25), decrease in tumor size was the best predictor for eventual tumor response (23). We used MRI-defined tumor size on the early post-contrast subtraction enhanced image in analysis, and the lesions with pCR showed significant size reduction after two cycles of neoadjuvant chemotherapy compared with those without pCR (P value, 0.045).

There are several limitations to our study. First, our sample size was small. Further studies in a large series are needed in the near future. Second, we did not evaluate the association of subtypes of breast cancer and pCR. Hayashi et al. has provided a correlation between molecular subtypes of breast cancer and the MRI capacity in predicting pCR (32). Diagnostic performances of MRI was said to differ among molecular subtypes of breast cancer and MRI was useful in predicting pCR, particularly in triple-negative tumors.

In conclusion, the lesion size and the degree of peak enhancement were significantly reduced in lesions with pCR after two cycles of neoadjuvant chemotherapy, but a large-scale study is anticipated.

Acknowledgement

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유방암 환자의 수술전 보조 항암화학요법 후 치료반응 예측에 있어 자기공명영상의 유효성

김가람 · 김은경 · 김민정 · 윤정현 · 문희정

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목적: 유방암 환자에서 수술 전 보조 항암화학요법 두 차례 후 시행한 역동 조영증강 자기공명영상과 확산자기공명영상이 병리적 완전관해를 예측할 수 있는가에 대하여 규명한다.

대상 및 방법: 14명의 유방암환자가 수술 전 보조 항암화학요법 2차례를 시행하기 전과 후에 역동 조영증강 자기공명영상과 확산자기공명영상을 동일한 자기공명영상 콘솔을 이용하여 촬영하였다. 2차례의 항암화학요법 전과 후에 역동 조영증강 자기공명영상의 병변에서 가장 강한 조영증강을 나타내는 부위의 크기, 가장 강한 조영증강 정도의 차이를 계산하고 확산자기공명영상에서 확산계수의 차이를 계산하였다. 추후 수술검체에서 병리적 완전관해를 보인 군과 보이지 않은 군 간에 상기 측정치의 차이와 변화를 비교하였다.

결과: 병변의 크기는 완전반응을 보인 군에서 그렇지 않은 군보다 더 작았다 (P value, 0.855). 완전반응을 보인 군에서 그렇지 않은 군보다 가장 강한 조영증강 정도와 확산계수가 더 낮았다 (P values, 0.770 and 0.660). 항암화학요법 후 병변의 크기와 조영증강 정도는 완전반응을 보인 군에서 그렇지 않은 군보다 통계적으로 유의하게 더 감소하였다 (P value, 0.045 and 0.044). 항암화학요법 후 병변의 확산계수는 완전반응을 보인 군에서 그렇지 않은 군보다 더 증가하였으나 통계적으로 유의하지는 않았다 (P value, 0.132).

결론: 보조 항암화학요법 두 차례 후 역동 조영증강 자기공명영상에서 병변의 크기와 가장 강한 조영증강 정도는 병리적 완전관해를 보인 군에서 유의하게 감소하였다. 추후 대규모의 연구가 필요하다.

Index words: Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI);
Diffusion weighted magnetic resonance imaging (DWI);
Pathologic complete response (pCR); Breast cancer; Neoadjuvant chemotherapy